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Propafenone During Acute Myocardial Ischemia in Patients: A Double-Blind, Randomized, Placebo-Controlled Study

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Objectives. **The proarrhythmic risk of class I antiarrhythmic agents in combination with myocardial ischemia is mainly the result of their effects on ventricular repolarization. This study was designed to evaluate the effect of class Ic antiarrhythmic agents on QT dispersion during myocardial ischemia.**

Background. **QT interval dispersion on the 12-lead electrocardiogram (ECG) has been suggested as a noninvasive marker of inhomogeneous ventricular repolarization and susceptibility to ventricular arrhythmias.**

Methods. **In a randomized, double-blind study, 98 patients undergoing percutaneous transluminal coronary angioplasty (PTCA) were pretreated with propafenone or placebo. QT dispersion was defined as a maximal minus minimal QT interval on the 12-lead ECG before and after PTCA. The power of the study to detect clinically meaningful differences in QT dispersion was 0.75, and a twofold increase in QT dispersion in the propafenone group compared with the placebo group was considered clinically relevant.**

Results. **The QT and corrected QT (QTc) intervals increased significantly during occlusion of the left anterior descending coronary artery (LAD) (9% and 11%, respectively, $p < 0.05$), whereas occlusion of the circumflex and right coronary arteries had no effect. QTc dispersion increased significantly in the propafenone group during ischemia (+52%, $p = 0.002$, vs. +23%, $p = 0.15$). The most considerable effect on QT dispersion was observed during LAD occlusion and ischemia of the anterior wall (+74%, $p = 0.025$). Corrected JT dispersion (+57%, $p = 0.017$, vs. +24%, $p = 0.23$) and the QT dispersion ratio (+1.6%, $p = 0.031$, vs. 0.9%, $p = 0.34$) showed similar effects. Plasma levels of propafenone (522 ± 165 μg/liter) did not influence the results.**

Conclusions. **During myocardial ischemia, particularly during LAD occlusion, propafenone results in a significant increase in QT dispersion. The results indicate that QT interval prolongation and enhanced QT dispersion reflect inhomogeneous ventricular repolarization generated by the ischemic anterior wall of the myocardium. These observations may demonstrate a clinically important interaction between myocardial ischemia, repolarization variables and propafenone.**

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Class I antiarrhythmic agents have been recognized as increasing the risk of sudden cardiac death when used in patients with coronary artery disease (1–4). More recently, increasing evidence has stressed the interaction of myocardial ischemia and class I antiarrhythmic activity (1,5–17) to explain the excess of sudden cardiac death mortality in the treatment arm of the Cardiac Arrhythmia Suppression Trial (CAST). This concept was supported by a recent subgroup analysis in the CAST population (18). However, very little is known of the beneficial or hazardous effects of class Ic antiarrhythmic activity in association with myocardial ischemia. Experimental data focusing on the conduction delay induced by both class Ic activity and myocardial ischemia demonstrated significant proarrhythmia due to a loss of antiarrhythmic efficacy and an increase in the heterogeneity of the repolarization process (7).

QT interval dispersion has been suggested as a noninvasive marker of such inhomogeneous ventricular repolarization (19–21) and susceptibility to ventricular arrhythmias, as has been shown in patients with the congenital long QT syndrome (22–31). Studies on the diagnostic impact of this variables also addressed patients with myocardial ischemia and infarction and those receiving antiarrhythmic therapy (19–21,31). However data on the combination of both myocardial ischemia and antiarrhythmic agents in patients are lacking.

In a prospective, double-blinded, randomized study, we assessed the effect of acute myocardial ischemia on ventricular repolarization dispersion (QT dispersion) on the surface electrocardiogram (ECG) in 98 patients pretreated with either placebo or propafenone while undergoing percutaneous transluminal coronary angioplasty (PTCA).

Methods

Patients. Ninety-eight patients were consecutively included in the study and randomized to receive either placebo (47

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Abbreviations and Acronyms

CAST = Cardiac Arrhythmia Suppression Trial
ECG = electrocardiogram, electrocardiographic
JTc = corrected JT interval
LAD = left anterior descending coronary artery
PTCA = percutaneous transluminal coronary angioplasty
QTc = corrected QT interval

patients) or propafenone (51 patients). There were 14 women and 84 men, with a mean [±SD] age of 59 ± 7 years (range 41 to 75). The study protocol was accepted by the local ethics committee, and written informed consent was obtained from all patients.

Patients were included in the study only when the following criteria were met: coronary artery disease with one or more stenotic lesion, lumen narrowing >75% and symptomatic and exercise-inducible myocardial ischemia giving the clinical indication for PTCA. Exclusion criteria for the study were age >75 years old, complete coronary artery occlusion, pretreatment with any antiarrhythmic agent, severe heart failure of New York Heart Association functional class IV, severe liver and kidney dysfunction, asthmatic disease, presence of atrial fibrillation, bundle branch block or first-degree or greater atrioventricular block.

The clinical data of all patients entered into the study are summarized in Table 1. No difference was seen between the two treatment groups regarding clinical characteristics or the presence, frequency and severity of myocardial ischemia before the study, severity of coronary stenotic lesions, exercise tolerance, ejection fraction or presence of heart failure. Ejection fraction in all patients was >35%.

Study design. Before entering the study, all patients underwent physical examination, chest radiography, echocardiography, 24-h Holter monitoring, exercise testing and PTCA. Twenty-four hour Holter monitoring and exercise testing were performed in all patients in a parallel design on the day before PTCA. Whenever possible, anti-ischemic medication (including beta-adrenergic blocking agents) was stopped at least 5 drug half lives before PTCA, except for short-acting nitrates. No further concomitant drug therapy was allowed during the study.

After inclusion in the study, patients were randomized to receive either placebo or propafenone. Both placebo and propafenone were given intravenously, starting 60 min before the start of PTCA. Patients randomized to receive propafenone received a bolus of 70 mg over 10 min followed by a maintenance infusion of 17.5 mg/h until the end of the PTCA. All patients were pretreated with 15,000 IU of heparin before PTCA. From blood samples that were obtained immediately before the first balloon inflation, the plasma concentration of propafenone was determined.

PTCA was performed in all patients by a standardized protocol. Whenever possible, the balloon inflation time was standardized to 60 s for the first attempt, 90 s for the second attempt and 120 s for the third and all following attempts. Simultaneous 12-lead surface ECGs were continuously recorded with a paper speed of 25 mm/s during the procedure and 50 mm/s before and until 5 min after balloon inflation. Time of onset and disappearance of symptoms of angina pectoris was documented during each PTCA attempt.

Table 1. Clinical and Angiographic Characteristics in the Two Study Groups*

	Propafenone Group (n = 51)	Placebo Group (n = 47)
Women/men	9/42	5/42
Age (yr)	59 ± 7	57 ± 8
History of infarction	30 (59%)	28 (60%)
Heart failure		
NYHA class ≤I	89 (82%)	5 (11%)
NYHA class II/III	9 (18%)	7 (15%)
Ejection fraction (%)	66 ± 15%	65 ± 14%
Angina pectoris	32 (63%)	29 (62%)
Episodes/wk	8 ± 13	6 ± 6
At rest	17 (33%)	15 (32%)
Risk factors		
Lipid disease	38 (75%)	28 (60%)
Smoking	32 (63%)	25 (53%)
Hypertensive disease	26 (51%)	23 (49%)
Family history	21 (41%)	23 (49%)
Adiposity	16 (31%)	7 (15%)
Diabetes mellitus	7 (14%)	6 (13%)
Coronary artery disease		
One vessel	26 (51%)	30 (64%)
Two vessel	17 (33%)	15 (32%)
Three vessel	6 (12%)	4 (9%)
No. of dilated stenotic lesions (1st PTCA)	55	55
LAD	24 (44%)	27 (49%)
Cx	10 (18%)	11 (20%)
RCA	13 (24%)	10 (18%)
Stenotic lesion (1st PTCA)	89 ± 7%	89 ± 9%
Total no. of PTCA attempts	137	135
Mean PTCA pressure (atm)	8.42 ± 2.64	8.65 ± 2.44
Residual stenosis	24 ± 10%	25 ± 11%
Plasma level of propafenone (μg/liter)	522 ± 165	
Range	223–896	

*p = NS for all comparisons. Data presented are mean value ± SD or number (%) of patients, unless otherwise indicated. Cx = circumflex coronary artery; LAD = left anterior descending coronary artery; NYHA = New York Heart Association functional class; PTCA = percutaneous transluminal coronary angioplasty; RCA = right coronary artery.

Assessment of ECG measurements. Data analysis was based on the first 60-s PTCA attempt. Data were obtained at baseline, after bolus injection and every 30 s starting with the onset of balloon inflation and ending 5 min after the onset of reperfusion. Electrocardiographic assessment included PQ, QRS, RR and QT intervals. Before and immediately after the end of balloon inflation (maximal ischemia), the QT interval and the interval between J point and the end of the T wave (JT interval) were manually measured on each of the 12 standard leads obtained with a recording speed of 50 mm/s. The

corrected QT (QTc) and JT (JTc) intervals were calculated using the Bazett formula. The QT interval was measured from the beginning of the QRS complex to the end of the T wave. The end of the T wave was defined visually as the point where the T wave returned to baseline. In case of a superimposed U wave, the QT interval was measured to the nadir between the T and U waves (32).

QT and QTc dispersion was defined as the difference between the minimal and maximal values on any of the 12 leads and was calculated from three consecutive complexes in all patients, except for one patient before and two patients after balloon inflation who had frequent ventricular ectopic activity, limiting QT measurement. *The QT dispersion ratio*, defined as QT dispersion divided by cycle length and expressed as a percentage, was also calculated at baseline and at the end of PTCA. The QT dispersion ratio was assessed according to a recently published report (19). ST segment changes as well as supraventricular and ventricular arrhythmias were also documented during the procedure. The measurements were made by two investigators (T.F., K.D.) who had no knowledge of the medication given to the patients. Intraobserver and interobserver variability and reproducibility of the QT measurements were evaluated in 10% of the study cohort. The incidence of a difference ≥15 ms was 3.9% and 5.1% of a total of 720 measurements considered for analysis during the study for both intraobserver and interobserver variability, respectively. The statistical power of the study to detect clinically meaningful differences between both groups was calculated to be 0.75.

Statistical analysis. Results are expressed as mean value ± SD. Data were compared before and after balloon inflation using a paired Student *t* test, two-way repeated measures analysis of variance and Mann-Whitney, chi-square and Wilcoxon tests where appropriate. A p value <0.05 was considered statistically significant.

Results

Clinical characteristics, baseline coronary artery anatomy and the results of therapeutic intervention were similar in the placebo and propafenone groups (Table 1).

Symptoms of angina pectoris and myocardial ischemia during coronary artery occlusion. Propafenone pretreatment was associated with a significantly higher incidence and earlier onset of symptoms of angina pectoris during acute coronary artery occlusion (time to onset 25 ± 20 s vs. 35 ± 20 s) and a significantly greater incidence, severity and duration of ischemic ST segment changes than placebo pretreatment when all PTCA attempts were considered (Table 2).

The PQ interval increased significantly only in the propafenone group (from 171 ± 22 to 181 ± 25 ms, $p < 0.05$) during balloon inflation. Conversely, the RR interval changed significantly in the placebo group (from 893 ± 159 to 834 ± 172 ms, $p < 0.05$) during transient coronary occlusion, whereas it remained unchanged in the propafenone group. However, PQ and RR intervals were not significantly different between both groups before and after balloon inflation. Mean QRS duration increased during acute ischemia slightly when the patient was pretreated with propafenone (from 93 ± 17 to 95 ± 17 ms); however, the difference was not significant compared with placebo pretreatment (from 94 ± 11 to 91 ± 12 ms, $p < 0.05$). Nevertheless, when a predefined increase in QRS duration >20% was chosen, of seven patients (7%) who met this criterion, six were in the propafenone group (mean QRS duration 132 ± 17 ms).

Table 2. Mean Changes in Clinical and Electrocardiographic Variables in Both Study Groups During Percutaneous Transluminal Coronary Angioplasty

	Propafenone Group	Placebo Group	p Value
Incidence of angina pectoris			
1st PTCA	26 (51%)	16 (34%)	0.650
All PTCA attempts	74 (54%)	59 (44%)	0.031
Incidence of ST segment depression			
1st PTCA	21 (41%)	18 (38%)	0.710
All PTCA attempts	70 (51%)	60 (44%)	0.027
Maximal ST segment depression (mV)			
1st PTCA	0.20 ± 0.10	0.20 ± 0.10	0.160
All PTCA attempts	0.27 ± 0.26	0.18 ± 0.09	0.028
Onset of ST segment depression (s)			
1st PTCA	11 ± 11	14 ± 13	0.280
All PTCA attempts	17 ± 9	21 ± 12	0.015
Duration of ST segment depression (s)			
1st PTCA	39 ± 16	49 ± 20	0.291
All PTCA attempts	68 ± 24	51 ± 17	0.024

Data presented are mean value ± SD or number (%) of patients. PTCA = percutaneous transluminal coronary angioplasty.

QT and QTc intervals and QT and QTc dispersion during acute myocardial ischemia. In both groups, mean QT and QTc intervals remained widely unchanged during coronary artery occlusion in any single lead. However, in leads reflecting the region of maximal ischemia, both mean QT and QTc intervals increased significantly in 69% (propafenone group) and 55% (placebo group) of patients during occlusion of the left anterior descending coronary artery (QT interval +11%: from 340 ± 46 to 379 ± 65 ms for propafenone vs. from 361 ± 78 to 399 ± 88 ms for placebo, $p < 0.05$; QTc interval +9%: from 417 ± 28 to 456 ± 35 ms for propafenone vs. from 411 ± 33 to 447 ± 39 ms for placebo, $p < 0.05$). However, in both treatment groups, lengthening of the QT and QTc intervals was of similar degree even in more distant leads (+9% vs. +8%, $p < 0.05$). In contrast, a slight, nonsignificant shortening of the QT and QTc intervals during balloon inflation was observed in only 30% of the placebo group and 12% of the propafenone group. In both treatment groups, no significant lengthening or shortening of the QT and QTc intervals occurred during occlusion of the circumflex and right coronary artery either in leads adjacent to the ischemic area or in more distant leads. Thus, both QT and QTc intervals were affected by the treated vessel rather than by lead selection and drug pretreatment. The effects of acute ischemia and propafenone on maximal and minimal QTc intervals are given in Figure 1. In patients pretreated with propafenone, a slight increase in

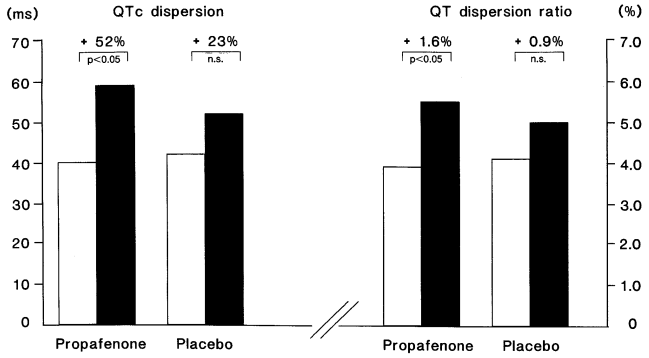

Figure 1. Mean QTc dispersion (ms) and QT dispersion ratio (%) in patients with myocardial ischemia treated with either propafenone or placebo at baseline **(open bars)** and after 60 s of coronary occlusion **(solid bars)**. Only propafenone significantly increased QTc dispersion and QT dispersion ratio.

the minimal QT interval was contrasted by a significant increase in the maximal QTc interval ($p < 0.001$) (Fig. 1). In contrast, in the placebo group a moderate increase was observed in both minimal and maximal QT intervals.

Results of the QTc dispersion analysis are summarized in Table 3. Sixty seconds of acute coronary artery occlusion resulted in a significant increase in the QTc dispersion time in the propafenone group by 42% ($p = 0.02$) compared to +14% ($p = 0.76$) in the placebo group. In both groups, the increase in QT dispersion time was related to the severity of myocardial ischemia; but in the presence of ST segment depression ≥0.15 mV, the increase was 2.3 times greater in the propafenone group (Table 3, Fig. 2). The most considerable increase in QT dispersion was observed in the propafenone group during occlusion of the LAD and ischemia of the anterior wall (+74%, from 35 ± 32 to 61 ± 27 ms, $p = 0.025$) compared with that in the placebo group (+14%, from 43 ± 17 to 49 ± 18 ms, $p = 0.8$). Compared with QTc dispersion time, JTc dispersion time analysis showed similar results in the propafenone (21 ± 41 ms, +57%, $p = 0.017$) and placebo groups (10 ± 39 ms, +24%, $p = 0.23$). Without correction for heart rate, a similar increase in QT dispersion of +38% (from 32 ± 26 to 44 ± 24 ms, $p < 0.05$) was observed in the propafenone group during balloon inflation, whereas no significant change occurred in the placebo group.

Of clinical variables analyzed, PTCA performed in the presence of left ventricular hypertrophy at baseline was a risk factor for an enhanced increase in the QTc dispersion time response to myocardial ischemia in the propafenone group. Presence and location of previous myocardial infarction had no different effect on QTc dispersion time response in the propafenone and placebo groups. However, patients with a previous myocardial infarction showed a significantly greater increase in QTc dispersion time during acute myocardial ischemia, and the differences were greatest in patients with a history of anterior versus inferior myocardial infarction (Table 3).

The mean plasma level of propafenone determined in blood samples taken immediately before balloon inflation (82 ±

Table 3. Mean Changes in Corrected QT Dispersion and QT Dispersion Ratio in Both Groups During Percutaneous Transluminal Coronary Angioplasty

	QTc Dispersion							
	Propafenone Group				Placebo Group			
	Baseline (ms)	End of PTCA (ms)	Mean QTd Increase	p Value	Baseline (ms)	End of PTCA (ms)	Mean QTd Increase	p Value
LAD, RCA, Cx occlusion in all patients	38 ± 28	54 ± 26	+42%	0.020	42 ± 23	48 ± 28	+14%	0.76
				p = 0.022				
LAD, RCA, Cx occlusion and ischemia*	40 ± 27	59 ± 26	+52%	0.002	42 ± 20	52 ± 30	+23%	0.15
				p = 0.048				
LAD occlusion and ischemia*	35 ± 32	61 ± 27	+74%	0.025	43 ± 17	49 ± 18	+14%	0.80
				p = 0.032				
LAD, RCA, Cx occlusion and hypertension	34 ± 26	52 ± 25	+53%	0.025	41 ± 23	49 ± 34	+20%	0.97
				p = 0.053				

	QT Dispersion Ratio							
	Propafenone Group				Placebo Group			
	Baseline	End of PTCA	Mean QTr Increase	p Value	Baseline	End of PTCA	Mean QTr Increase	p Value
All patients	3.9 ± 2.9%	5.5 ± 2.9%	+1.6% (+41%)	0.031	4.1 ± 2.4%	5.0 ± 3.5%	+0.9% (+21%)	0.340

*ST segment depression <0.15 mV. Data presented are mean value ± SD, unless otherwise indicated. QTc = corrected QT interval; QTd = QT interval dispersion; QTr = QT dispersion ratio; other abbreviations as in Table 1.

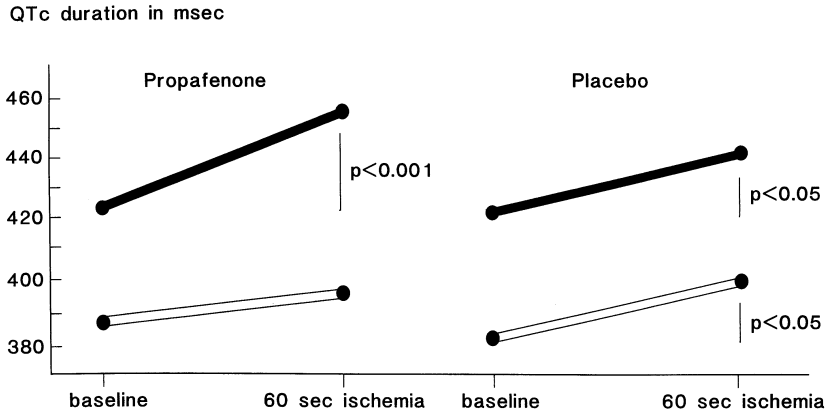

Figure 2. Maximal (**solid lines**) and minimal QTc duration (**open lines**) in patients treated with either propafenone or placebo at baseline and after 60 s of myocardial ischemia. There was no difference in minimal QTc duration, but a significant increase in QTc maximal duration, in patients pretreated with propafenone ($p < 0.001$).

32 min after the first bolus injection of 70 mg) was 522 ±165 μg/liter (range 223 to 896). No statistically significant relation was found between the plasma level of propafenone and QT variables during myocardial ischemia. In particular, no difference was observed between the propafenone plasma concentration in patients with occlusion of the LAD and the most pronounced changes in QT measures and those with occlusion of the right and circumflex coronary arteries and fewer changes in QT variables (528 ± 161 vs. 512 ± 175 μg/liter, respectively, $p = 0.27$).

QT dispersion ratio increased when myocardial ischemia was induced by PTCA in both study groups; however, the effect was significantly greater in the propafenone group (+41%, $p = 0.031$) than in the placebo group (+21%, $p = 0.34$). In patients without ischemic ST segment alteration, the QTc and JTc dispersion times as well as the QT dispersion ratio remained unchanged (Table 3, Fig. 2).

Ventricular tachyarrhythmias during coronary artery occlusion. Before PTCA, 24-h Holter recording of the incidence of ventricular arrhythmias (propafenone: 41 [80%] of 51 patients; placebo: 45 [96%] of 47 patients, $p > 0.05$), frequent ventricular arrhythmias (>100/24 h) (propafenone: 11 patients [22%], placebo: 11 patients [23%]) and ventricular pairs (propafenone: 9 patients [18%], placebo: 9 patients [19%]) or salvos/tachycardia (propafenone: 5 patients [10%], placebo: 1 patient [2%]) were similar in the two study groups.

During acute coronary artery occlusion, ventricular arrhythmias were observed in 9 patients (18%) in the propafenone group and 19 (38%, $p < 0.05$) in the placebo group. Repetitive, nonsustained ventricular arrhythmias were observed in only two patients in the placebo group. In no patient did sustained tachyarrhythmias, including torsade de pointes arrhythmias, occur during coronary occlusion.

Discussion

The use of antiarrhythmic drugs in patients with ventricular tachyarrhythmias carries a 2% to 15% risk for clinically manifest proarrhythmia (1,5,11). This risk seems particularly high when class I antiarrhythmic agents are given to patients with ischemic heart disease (2–4). In those patients, myocardial ischemia itself is common and is already known to carry a substantial risk for inducing or aggravating ventricular tachyarrhythmias (6,33). In addition, the interaction between myocardial ischemia, ventricular arrhythmias and class I antiarrhythmic drugs has been proved in both experimental (12,14,34–36) and clinical studies (8,10,37–42). Class Ic agents have particularly been shown to slow ventricular impulse propagation and to increase ischemia-induced nonuniform ventricular repolarization (7), which is considered a potential prerequisite for subsequent arrhythmic events (14,24).

QT dispersion. The clinical significance of QT interval dispersion as a noninvasive variable for inhomogeneous ventricular repolarization and predictor for ventricular arrhythmias has been evaluated in both ischemic heart disease and antiarrhythmic drug treatment (19–21,28,31,43,44). Several studies demonstrated that an increased QT interval dispersion after acute myocardial infarction (23,31,45) is predictive for subsequent arrhythmic events during the follow-up period (19). A close relation between administration of class I antiarrhythmic drugs, increased QT dispersion and subsequent tachyarrhythmic events, mostly classified as torsade de pointes, has also been shown even in the absence of myocardial ischemia (20). Conversely, class III antiarrhythmic drugs, such as amiodarone (20,46) and sotalol (26), had no negative effects on, or even reduced, QT dispersion when studied in the same patients.

The present study used a double-blind, placebo-controlled design, and, to our knowledge, is the first to evaluate the effects of myocardial ischemia on QT dispersion variables in a large group of patients pretreated with a class Ic antiarrhythmic agent. The power of the study to detect clinically meaningful differences was 0.75, and a twofold increase in the difference of QT dispersion in the propafenone group during PTCA compared with the placebo group was considered clinically relevant. The study showed that intravenous administration of propafenone during acute coronary occlusion results in a

significant 2.5-fold increase in dispersion of QT/QTc and JT/JTc measures over that with placebo administration.

As an important result, the study also showed that dispersion of QT/QTc and JT/JTc intervals in the propafenone group was considerably higher with acute LAD occlusion and ischemic reaction of the anterior wall (+74%, p = 0.025) than circumflex and right coronary artery occlusion. The effects on dispersion variables were also found to be more pronounced for a previous anterior wall infarction than for an inferior wall infarction. Our results, which are consistent with others (45), demonstrate the important influence of the site of coronary occlusion on assessment of QT interval prolongation and QT dispersion on the standard 12-lead ECG. The findings suggest that measures of the ventricular repolarization process on the 12-lead ECG, as used in the present study, are mainly influenced by ischemic changes in the anterior wall of the myocardium, which is adjacent to the recording leads. In addition, the greater ischemic zone commonly resulting from LAD occlusion than from circumflex or right coronary artery occlusion will further influence this factor. This observation may be of particular significance for the methodologic approach when assessing patients with coronary artery disease. The QT dispersion ratio (19), another repolarization variable, could not be proved superior to the conventional method in assessing repolarization abnormalities during acute myocardial ischemia.

QT interval and conduction. The negative effect of propafenone on ventricular repolarization during myocardial ischemia was not assessable by measuring the QT interval in any single lead. However, a significant QT and QTc prolongation was observed in ~60% of patients when more than one lead was considered. Mean QT/QTc prolongation was similar in both leads reflecting the ischemic area and in more distant leads and overall was most pronounced during occlusion of the LAD. This finding suggests that the total amount of ischemic myocardium contributes most to the repolarization pattern assessed in any lead on the surface ECG (45).

When the shortest and longest mean QT intervals were analyzed in the two study groups, there was only a slight difference in minimal QTc interval in patients pretreated with propafenone, whereas maximal QTc interval increased significantly when acute ischemia was induced. Thus, QTc/JTc dispersion resulting from the combination of class I antiarrhythmic activity and acute ischemia was largely generated by prolongation of the maximal QTc/JTc interval, an observation that was also made in patients with unstable angina and acute myocardial infarction with and without ventricular fibrillation (19).

In six patients, all with a previous myocardial infarction, the predefined criterion for QRS broadening of >20% of the baseline value was observed when acute ischemia and propafenone pretreatment were present. It is likely that the observed increase in QRS duration reflects use-dependent sodium channel blockade. However, because the increase in QRS duration occurred during myocardial ischemia, the interaction of propafenone and myocardial ischemia must also be considered an important factor for QRS prolongation, a potential risk factor for facilitating nonuniform ventricular recovery (1,18).

Despite the finding that the overall incidence of nonsustained and sustained ventricular arrhythmias in both groups was low or did not occur, singular ventricular ectopic beats were less common in the propafenone group. Although this may be partly due to the known antiarrhythmic properties of propafenone, the CAST trial clearly demonstrated the adverse and proarrhythmic effects of other class Ic agents (flecainide, encainide) that have previously been shown to successfully suppress ventricular arrhythmias (1,18). Thus, even if an antiarrhythmic drug suppresses ventricular arrhythmias, it may also exert proarrhythmic activity. In the present study, no dangerous arrhythmias occurred in the propafenone group during PTCA, although repolarization abnormalities increased significantly. A longer duration of acute ischemia obviously may have enhanced these effects and may have provoked malignant arrhythmias. However, due to the ethical responsibility of the investigators, this was not done. Although the duration of myocardial ischemia in the present study was relatively short, the model was nevertheless effective in demonstrating a synergistic effect of acute ischemia and class I antiarrhythmic activity on ventricular repolarization; thus, the observations of the present study are of particular clinical importance. Plasma concentrations of propafenone, determined immediately before balloon inflation, were found to be in the therapeutic range, and no significant relation between plasma levels and measurements of QT variables was observed. This finding also confirms clinical findings that antiarrhythmic and adverse effects of propafenone do not correlate adequately with plasma concentrations. This lack of correlation has been explained by the nonlinear dose–plasma concentration relation of propafenone, predominantly in subjects with an extensive metabolizer phenotype, due to its marked hepatic first-pass metabolism through a saturable oxidative elimination pathway (47,48).

Conclusions. To our knowledge, the present study is the first to provide data on the effect of class Ic antiarrhythmic agents in patients with ischemic episodes. A twofold increase in the difference of QT dispersion in the study group during coronary occlusion was considered clinically meaningful; thus, the study demonstrated that in the setting of myocardial ischemia, particularly in the anterior wall during LAD occlusion, propafenone resulted in a significant increase in QT interval dispersion, suggesting a nonuniform recovery of the ventricle. The study further suggests that dispersion of QT measures on the 12-lead ECG predominantly reflects abnormal ventricular repolarization generated by ischemia in the anterior wall of the myocardium, which may be of particular importance for assessing patients with coronary artery disease.

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